**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 49/00 — A2

(11) International Publication Number: **WO 98/52617**

(43) International Publication Date: 26 November 1998 (26.11.98)

(21) International Application Number: PCT/GB98/01489

(22) International Filing Date: 22 May 1998 (22.05.98)

(30) Priority Data:
9710604.1 22 May 1997 (22.05.97) GB

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/049,174 (CIP)
Filed on 9 June 1997 (09.06.97)

(71) Applicant *(for all designated States except US)*: NYCOMED IMAGING AS [NO/NO]; Nycoveien 1–2, N–0401 Oslo (NO).

(71)(72) Applicant and Inventor *(for GB only)*: COCKBAIN, Julian [GB/GB]; 27 Ladbroke Road, London W11 3PD (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MCINTIRE, Gregory, Lynn [US/US]; Nycomed Inc., 466 Devon Park Drive, Wayne, PA 19087–8630 (US). TONER, John, Luke [US/US]; Nycomed Inc., 466 Devon Park Drive, Wayne, PA 19087–8630 (US). BACON, Edward, Richard [US/US]; Nycomed Inc., 466 Devon Park Drive, Wayne, PA 19087–8630 (US). HAYLEY, Patrick, Joseph [US/US]; Nycomed Inc., 466 Devon Park Drive, Wayne, PA 19087–8630 (US).

(74) Agents: COCKBAIN, Julian et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*Without international search report and to be republished upon receipt of that report.*

(54) Title: CONTRAST MEDIA

(57) Abstract

The invention relates to the use of particulate contrast media in the *in vivo* imaging of lung draining lymph nodes, e.g. to stage lung cancer patients.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **AL** | Albania | **ES** | Spain | **LS** | Lesotho | **SI** | Slovenia |
| **AM** | Armenia | **FI** | Finland | **LT** | Lithuania | **SK** | Slovakia |
| **AT** | Austria | **FR** | France | **LU** | Luxembourg | **SN** | Senegal |
| **AU** | Australia | **GA** | Gabon | **LV** | Latvia | **SZ** | Swaziland |
| **AZ** | Azerbaijan | **GB** | United Kingdom | **MC** | Monaco | **TD** | Chad |
| **BA** | Bosnia and Herzegovina | **GE** | Georgia | **MD** | Republic of Moldova | **TG** | Togo |
| **BB** | Barbados | **GH** | Ghana | **MG** | Madagascar | **TJ** | Tajikistan |
| **BE** | Belgium | **GN** | Guinea | **MK** | The former Yugoslav Republic of Macedonia | **TM** | Turkmenistan |
| **BF** | Burkina Faso | **GR** | Greece | | | **TR** | Turkey |
| **BG** | Bulgaria | **HU** | Hungary | **ML** | Mali | **TT** | Trinidad and Tobago |
| **BJ** | Benin | **IE** | Ireland | **MN** | Mongolia | **UA** | Ukraine |
| **BR** | Brazil | **IL** | Israel | **MR** | Mauritania | **UG** | Uganda |
| **BY** | Belarus | **IS** | Iceland | **MW** | Malawi | **US** | United States of America |
| **CA** | Canada | **IT** | Italy | **MX** | Mexico | **UZ** | Uzbekistan |
| **CF** | Central African Republic | **JP** | Japan | **NE** | Niger | **VN** | Viet Nam |
| **CG** | Congo | **KE** | Kenya | **NL** | Netherlands | **YU** | Yugoslavia |
| **CH** | Switzerland | **KG** | Kyrgyzstan | **NO** | Norway | **ZW** | Zimbabwe |
| **CI** | Côte d'Ivoire | **KP** | Democratic People's Republic of Korea | **NZ** | New Zealand | | |
| **CM** | Cameroon | | | **PL** | Poland | | |
| **CN** | China | **KR** | Republic of Korea | **PT** | Portugal | | |
| **CU** | Cuba | **KZ** | Kazakstan | **RO** | Romania | | |
| **CZ** | Czech Republic | **LC** | Saint Lucia | **RU** | Russian Federation | | |
| **DE** | Germany | **LI** | Liechtenstein | **SD** | Sudan | | |
| **DK** | Denmark | **LK** | Sri Lanka | **SE** | Sweden | | |
| **EE** | Estonia | **LR** | Liberia | **SG** | Singapore | | |

# CONTRAST MEDIA

This invention relates to contrast agents for imaging of the lung draining lymph nodes, and to methods of in vivo imaging of lung draining lymph nodes.

Lung cancer is responsible for a major proportion of cancer diagnoses, representing some 200000 new cases per year in the USA alone. Suspected and confirmed cases are staged by CT (X-ray) scanning of lymph nodes with the physician looking at the size of the nodes. Big nodes are assumed to contain metastatic disease while smaller nodes are assumed to be disease free. This however is by no means always the case. Large lymph nodes may simply be inflamed and not cancerous while small nodes can be infiltrated with metastatic cells. Accordingly, the patients' treatment and prognosis is often decided upon relatively inaccurate information. Besides CT-scanning, the only other conventional diagnostic check is mediastinoscopy, a surgical procedure which involves removal of the mediastinal lymph nodes and histopathologic assessment of disease state. This surgical procedure is usually only done efficiently at large tertiary cancer centres.

There is thus a need for alternative, more effective means for assessing the status of the lung draining lymph nodes and so providing better staging of the extent of disease in lung cancer patients.

We have now found that after administration of insoluble particulate contrast agents into the lungs it is possible to visualize adequately the lung draining lymph nodes in in vivo diagnostic imaging procedures in order to stage lung cancer.

Thus viewed from one aspect the invention provides a method of in vivo imaging of lung draining lymph nodes, said method comprising administering into the lung of an air breathing animal (e.g. a human or other

mammal, or a reptile or bird), e.g. by direct instillation into the airways of the deep lung or at or near sites of particular interest, a diagnostically effective amount of a physiologically tolerable, substantially water-insoluble, particulate contrast agent, and after a period of time sufficient for uptake of particles of said contrast agent by lung draining lymph nodes generating an image of at least part of the lungs of said animal, e.g. by using an X-ray, MR, nuclear or ultrasound diagnostic imaging modality.

Viewed from a further aspect the invention provides the use of a physiologically tolerable, substantially water-insoluble, particulate contrast agent for the manufacture of a diagnostic contrast agent composition for use in a method of diagnosis involving administration of said composition into the lungs of an air-breathing animal and, after a period of time sufficient for uptake of particles of said contrast agent by lung draining lymph nodes, generating an image of at least part of the lungs of said animal.

Viewed from a further aspect the invention provides a contrast agent composition for use in a method of diagnosis involving administration of said composition into the lungs of an air-breathing animal and after a period of time sufficient for uptake of particles of said contrast agent by lung draining lymph nodes generating an image of at least part of the lungs of said animal, said composition comprising a physiologically tolerable, substantially water-insoluble, particulate contrast agent together with at least one physiologically tolerable carrier or excipient, e.g. a gas or gas-precursor or a liquid.

Viewed from a yet further aspect the invention provides a contrast agent composition package comprising an aerosol or powder dispenser containing a physiologically tolerable substantially water-insoluble, particulate contrast agent optionally together with at

least one physiologically tolerable carrier or excipient, e.g. a gas or gas-precursor or a liquid such as water.

The particulate contrast agent used according to the invention may be particles of any substantially water-insoluble, physiologically tolerable material capable of enhancing contrast in the diagnostic imaging modality of choice. The particles may be liquid droplets or flexible vesicles but more preferably will be solid particles. By substantially water-insoluble is meant that the particles do not dissolve in the lung fluids to any significant extent, e.g. particles of up to 1% which by weight dissolves in water at 37°C in 10 days. The particle size should desirably be as uniform as possible, e.g. 90% or more by number should desirably be within 10% of the numerical mean particle size, ie. substantially monodisperse. The mean particle size will desirably be in the range 1 to 10000nm, preferably 5nm to 1μm, especially preferably 8 to 400nm. Such particles can be prepared by precipitation or emulsification techniques or by milling.

Where the diagnostic imaging modality is X-ray (e.g. CT-scanning), the particles will desirably be of an iodine or heavy metal (i.e. atomic number 37 or greater) containing material, e.g. a bismuth, tungsten or barium compound such as barium sulphate or a solid or liquid iodinated compound (e.g. triiodophenyl compound) as discussed in US-A-5330739, US-A-5318768, US-A-5310537, US-A-5308607, US-A-5312616, US-A-5316755, US-A-5260049, US-A-5326553, US-A-5310538, US-A-5260478, US-A-5318767 and US-A-5264610. For use in MR imaging, the contrast agent is preferably an inorganic ferromagnetic, ferrimagnetic, superparamagnetic or paramagnetic material optionally provided with a coating or matrix material, e.g. a polymeric coating such as a silane or polystyrene. Nanometer sized iron oxide particles, i.e. SPIO's or USPIO's, namely particles of the type present

in Nycomed's ABDOSCAN product or Advanced Magnetic's Biomag M4200 product or as described in PCT/GB97/00067 may thus be used. Alternatively, particles of gadolinium oxalate or another relatively insoluble paramagnetic compound may be used. Furthermore, paramagnetic metal compound loaded molecular sieve particles (e.g. particles of the type used in Gadolite) may be used. Similarly, insoluble particles of gadolinium loaded polychelants, e.g. loaded dendrimeric macrocyclic chelant carrying compounds (see for example WO93/06868), may be used. For ultrasound imaging any echogenic material may be used as a contrast agent and these may, for example, be particles of greater or lesser density than the body fluid in the lymph nodes, e.g. inorganic particulates (e.g. barium sulphate) or gas filled synthetic polymer capsules. Suitable gases are described in PCT/GB97/00459 and WO-96/40285 (Unger). Preferred as gases are air, perfluorobutane and perfluoropentane. The capsule material may be any biotolerable polymer or cross-linked membrane forming material, see for example WO93/17718 and EP-A-458745. For other imaging modalities, appropriate contrast enhancing substances may be used.

Preferably the contrast agent is an X-ray contrast agent and in particular an insoluble, solid (at 37°C) iodinated compound.

The contrast agent will generally be administered as a dry powder dust or as a liquid aerosol and conventional liquid suspension media, e.g. water for injections, saline, phosphate buffered saline, and mixed aqueous/non-aqueous solvent systems (eg. aqueous alkanolic solutions) may be used. If desired the compositions administered may contain further components, such as stabilizers (e.g. polyalkylene oxides, such as pluronics), surfactants, dispersants, pH and osmolality adjusting agents, antioxidants and the like. Thus the composition administered may be entirely

composed of contrast agent or may for example contain as little as 0.001% w/w contrast agent. The actual content clearly will depend on the imaging modality used. However, generally the composition will contain 1 to 99% w/w contrast agent, more preferably 10-70%, for CT and X-ray imaging procedures.

The contrast agent, or the composition containing the contrast agent, may be filled into inhaler devices of the type conventionally used for administration of dry powders or aerosols into the lungs. Preferably these devices will be metered inhalers so that a pre-determined amount of contrast agent is delivered per activation. The required contrast agent dosage may then be delivered by multiple activations of the device. Devices of the kind disclosed in WO96/19253, WO96/04948, WO92/10229 and WO92/09323 are preferred.

Alternatively, and more preferably, the contrast agent may be instilled directly into the lungs via a tube inserted through the mouth or nose. Direct instillation via bronchoscopy into the deep lung or to the region of a lesion of interest is preferred. Again the contrast agent will preferably be delivered as a dry powder or an aerosol spray, or as a liquid suspension.

The total dosage of contrast agent required will clearly depend on the subject under study and the imaging modality used. Generally however contrast agent dosages will be 0.1 to 500 mg/kg bodyweight, preferably 0.1 to 200 mg/kg, or $10^5$ to $10^{20}$ particles/kg bodyweight, preferably $10^7$ to $10^{15}$ particles/kg. For X-ray imaging the dosage will preferably be in the range 20 to 400 mg/kg, more preferably 60 to 200 mg/kg; for MR imaging with paramagnetic particulates 0.1 to 10 mmol paramagnetic metal/kg; for MR imaging with superparamagnetic particles 1 to 100 mg/kg; for ultrasound imaging with inorganic particulates 0.1 to 100 mg/kg, more preferbly 1 to 20 mg/kg; and for ultrasound imaging with gas or gas precursor containing

particles (e.g. vesicles, micelles, liposomes, microballoons, etc.) 0.1 to 100 mg/kg, more preferably 1 to 20 mg/kg.

Image generation will suitably be effected after contrast agent transport to the lung draining lymph nodes has occurred, e.g. 120 mins to 60 days, preferably 2 to 40 days, especially preferably 6 to 20 days after contrast agent administration. For most insoluble particulates image generation may be effected after even longer delays, e.g. up to 60 days. It is preferred that the delay before image generation is sufficient to allow substantial particle clearance from the lungs e.g. via the mucociliary pathway; in humans a delay of at least about 4 days is preferred.

The image generation may be by conventional techniques, e.g. X-ray CT, B-mode ultrasound, spin-echo MRI, etc. For gas-containing contrast agents, e.g. with envelopes similar to that in Schering AG's Cavisome product, increased ultrasound intensity may be used to burst particles contained in the lymph nodes and the ultrasound signal from the bursts may be imaged using the "popcorn" technique.

If desired, the contrast agent may be delivered together with a therapeutic agent (e.g. a cytotoxic or gene therapy agent) where lung cancer has already been diagnosed. In this way the delivery of the therapeutic agent and the progress of therapy may be monitored using the technique of the invention. If this is to be done the therapeutic agent, e.g. cisplatin, may be in dissolved or more preferably particulate form and if particulate it and the contrast may be in the same or different particles. Thus for example a therapeutic agent may be encapsulated within a contrast agent which is in vesicle form, it may be coated onto or in the pores of a contrast agent in solid form, or it may be bound to the surface of a contrast agent particle. The dosage of therapeutic agent required will be dependent

on the particular agent chosen and may for example be the same or less than the conventional dosage for the selected agent.

Such combined imaging and therapy, and the compositions for use therein, form further aspects of the present invention.

Thus viewed from a further aspect the invention provides a method of imaging and treatment of lung cancer, said method comprising administering into the lungs of an affected animal a particulate composition comprising therapeutically and diagnostically effective amounts of a therapeutic agent and a physiologically tolerable, substantially water-insoluble, particulate contrast agent and after a period of time sufficient for uptake of particles of said contrast agent by lung draining lymph nodes generating an image of at least part of the lungs of said animal, e.g. by using an X-ray, MR, nuclear or ultrasound diagnostic imaging modality.

The use of direct instillation to administer particulate therapeutic agents into the lung, e.g. to the region of a lesion of interest within the lung or to the deep lung, is also a further aspect of the invention. Thus viewed from another aspect the invention provides a method of treatment of the human or non-human animal body comprising direct instillation of a particulate therapeutic agent into the lung of said animal e.g. to the region of a lesion of interest within the lung or to the deep lung.

Such therapy will be advantageous since, unlike subcutaneous injection where most of the dose remains for a time at the injection site, direct instillation in the lung will be followed by rapid dispersion within the lung due to the presence of the lung surfactant itself and movement out of the lung via the bronchociliary pathway.

The resolution of the image generated using the

method of the invention will be dependent upon imaging modality and dose. CT-X-ray enables both morphology and filling defects in the lymph nodes to be imaged in vivo at or below millimetre dimensions. MRI will allow excellent contrast at particle dosage levels below those required for CT. This will also be true of radiopharmaceuticals (containing longer lived isotopes such as indium or iodine isotopes, rather than technecium) used in nuclear medicine imaging techniques, e.g. gamma imaging.

The publications referred to herein are hereby incorporated by reference.

The invention will now be described further with reference to the following non-limiting examples, and to the accompanying drawings in which:

Figure 1 is a schematic diagram of the lungs in the dog; and Figures 2 and 3 are X-ray CT images of the dog lung at 9 and 16 days post contrast administration.

Example 1

CT Suspension

| | | |
|---|---|---|
| Nanoparticulate NC 70146* | | 75mgI/mL |
| Pluronic F68 | | 3.5% w/v |
| Water for injections | ad | 100% w/w |

* An insoluble iodinated compound prepared as described in Example 3 of US-A-5525328, particle size 132 ± 40 nm

Example 2

CT Suspension

| | | |
|---|---|---|
| Nanoparticulate NC 70146* | | 75mgI/mL |
| Pluronic F108 | | 3.0% w/v |
| Water for injections | ad | 100% w/w |

* An insoluble iodinated compound prepared as described in Example 3 of US-A-5525328, particle size 127 ± 45 nm

Example 3

Three beagle dogs were instilled with the suspension of Example 1. The instillations were carried out via bronchoscope as follows: 1.5ml in the lower left lobe, 3 x 1.5ml in the right lower lobe, 1.5ml vehicle only in the small, central lower lobe, and 1.5ml of saline in the upper left lobe. (See Figure 1). The instillations were video taped via the bronchoscope with no adverse events associated with the instillation. Immediately after instillation, the anaesthetized dogs were imaged by conventional X-ray to view the placement of the test agent. The dogs were then returned to their cages. Thereafter, the dogs were imaged by Computed Tomography (CT). The imagings were carried out at days 2, 9 and 16 post instillation using standard clinical settings for small child, thoracic scan (120 kV, pitch = 1) on a Picker spiral CT scanner. The dogs were again imaged by conventional X-ray and sacrificed on day 17 for morphologic and histopathologic evaluation of the lung tissues.

Images of days 9 and 16 appear as Figures 2 and 3 hereto.

The results of these studies were:

1. A complete absence of adverse events during the instillations and the in life phase of the study.
2. Clear visualization of the test article at the instillation site via conventional X-ray at instillation. CT confirmation at day 2. Only lung windowed images demonstrated test article at the instillation site by day 9. Clearance from the instillation site was complete before the final imaging on day 16.
3. Increasing CT opacification of the tracheo-bronchial lymph nodes with time; minimal enhancement at day 2, moderate enhancement at day 9, excellent enhancement at day 16 post instillation.

4. No evidence of residual test article at the instillation site by either conventional X-ray at day 17 or CT scans at day 16.
5. Minimal observations at sacrifice of small, residual amounts of nanoparticle test agent on the surface of the lung near the original instillation sites. No macroscopic observations of tissue damage, inflammation, or necrosis/fibrosis were noted at necropsy.

Example 4

Three beagle dogs were instilled with the suspension of Example 2. The instillations were carried out via bronchoscope as follows: 1.5ml in the lower left lobe, 3 x 1.5ml in the lower right lobe, 1.5ml vehicle only in the small, central lower lobe, and 1.5ml of saline in the upper left lobe. (See Figure 1). The instillations were video taped via the bronchoscope with no adverse events associated with the instillation. Immediately after instillation, the anaesthetized dogs were imaged by conventional X-ray to view the placement of the test agent. The dogs were then returned to their cages. Thereafter, the dogs were imaged by Computed Tomography (CT). The imagings were carried out at days 6, 13 and 34 post instillation using standard clinical settings for a small child, thoracic scan (100 kV, pitch = 1) on a Picker spiral CT scanner. The dogs were again imaged by conventional X-ray and sacrificed on day 35 for morphologic and histopathologic evaluation of the lung tissues.

Results in this study are:

1. Excellent imaging at both day 6 and 13 post instillation.
2. A complete absence of any adverse events during or after instillation.
3. No observation of residual test article at the instillation site by day 13.

CLAIMS:

1. A method of in vivo imaging of lung draining lymph nodes, said method comprising administering into the lung of an air breathing animal a diagnostically effective amount of a physiologically tolerable, substantially water-insoluble, particulate contrast agent, and after a period of time sufficient for uptake of particles of said contrast agent by lung draining lymph nodes generating an image of at least part of the lungs of said animal.

2. A method as claimed in claim 1 wherein said contrast agent is administered by direct instillation into the airways of the deep lung or at or near sites of particular interest.

3. A method as claimed in claim 1 wherein said image is generated by an x-ray, MR, nuclear or ultrasound imaging modality.

4. A method as claimed in claim 1 wherein said contrast agent is an iodinated organic compound.

5. The use of a physiologically tolerable, substantially water-insoluble, particulate contrast agent for the manufacture of a diagnostic contrast agent composition for use in a method of diagnosis involving administration of said composition into the lungs of an air-breathing animal and, after a period of time sufficient for uptake of particles of said contrast agent by lung draining lymph nodes, generating an image of at least part of the lungs of said animal.

6. Use as claimed in claim 5 wherein said contrast agent is an iodinated organic compound.

7. A contrast agent composition for use in a method of diagnosis involving administration of said composition into the lungs of an air-breathing animal and after a period of time sufficient for uptake of particles of said contrast agent by lung draining lymph nodes generating an image of at least part of the lungs of said animal, said composition comprising a physiologically tolerable, substantially water-insoluble, particulate contrast agent together with at least one physiologically tolerable carrier or excipient.

8. A contrast agent composition package comprising an aerosol or powder dispenser containing a physiologically tolerable substantially water-insoluble, particulate contrast agent optionally together with at least one physiologically tolerable carrier or excipient.

9. A method of imaging and treatment of lung cancer, said method comprising administering into the lungs of an affected animal a particulate composition comprising therapeutically and diagnostically effective amounts of a therapeutic agent and a physiologically tolerable, substantially water-insoluble, particulate contrast agent and after a period of time sufficient for uptake of particles of said contrast agent by lung draining lymph nodes generating an image of at least part of the lungs of said animal.

10. A pharmaceutical composition comprising an anticancer agent and a physiologically tolerable, substantially water-insoluble, particulate contrast agent.

11. A method of treatment of the human or non-human animal body comprising direct instillation of a

particulate therapeutic agent into the lung of said animal.

12. A method as claimed in claim 11 wherein said agent is instilled to the region of a lesion of interest within the lung or to the deep lung.

PULMONARY DELIVERY

SCHEMATIC DIAGRAM OF DOG LUNG

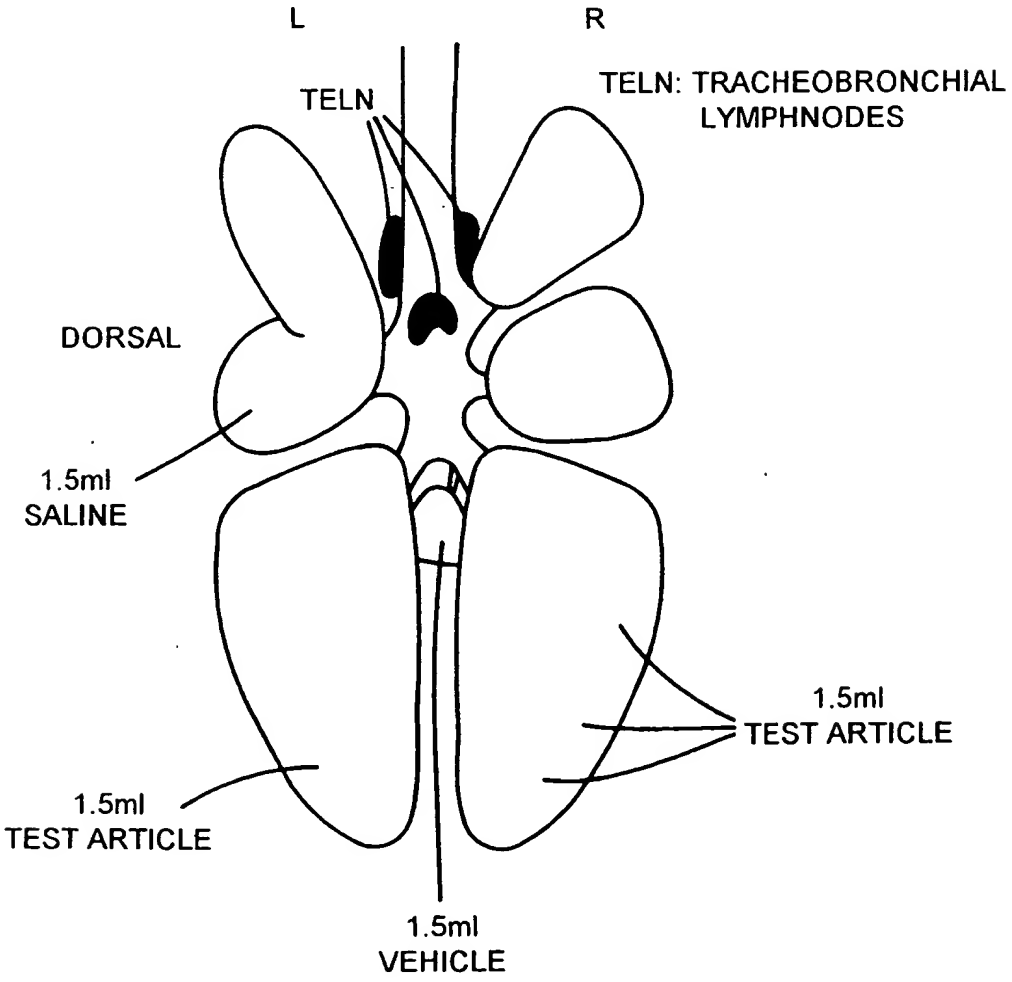



FIG. 1

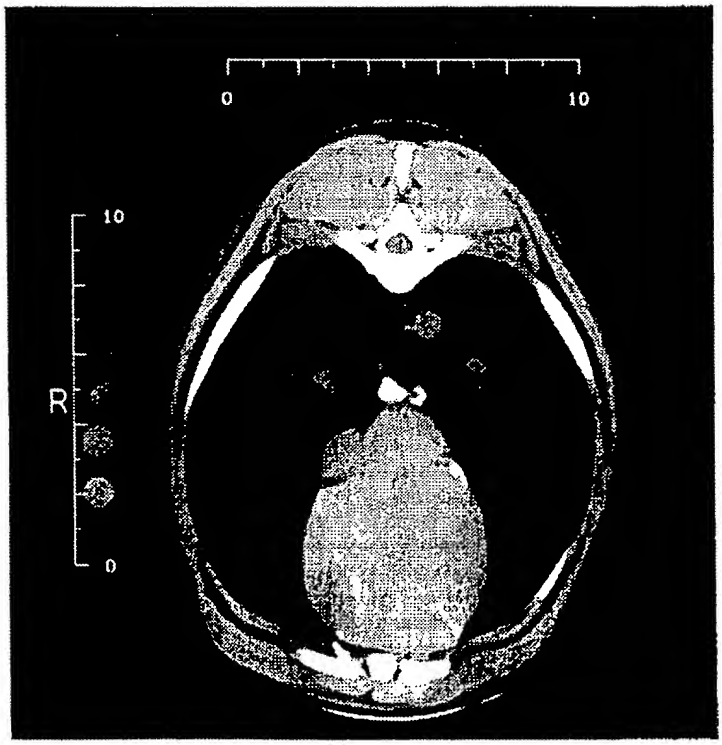



FIG. 2

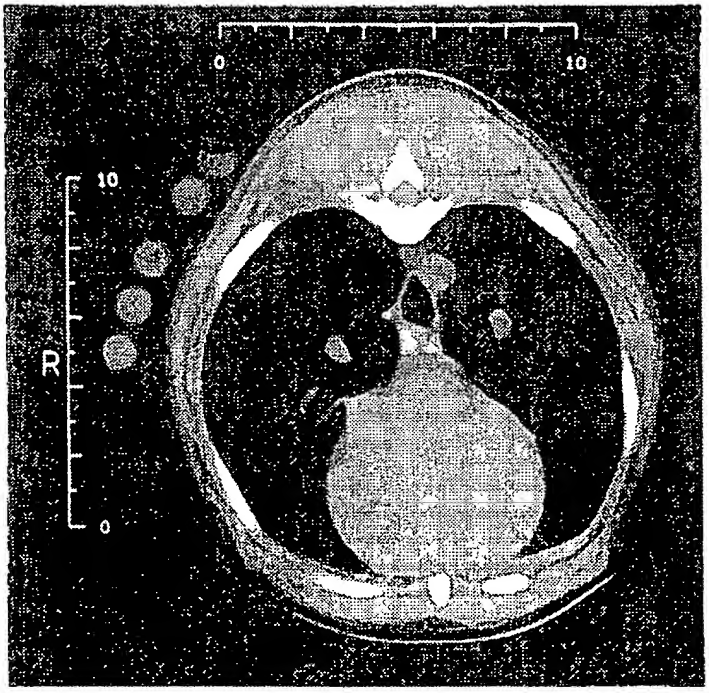



FIG. 3

**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 49/04

A3

(11) International Publication Number: **WO 98/52617**

(43) International Publication Date: 26 November 1998 (26.11.98)

(21) International Application Number: PCT/GB98/01489

(22) International Filing Date: 22 May 1998 (22.05.98)

(30) Priority Data:
9710604.1 22 May 1997 (22.05.97) GB

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/049,174 (CIP)
Filed on 9 June 1997 (09.06.97)

(71) Applicant *(for all designated States except US)*: NYCOMED IMAGING AS [NO/NO]; Nycoveien 1-2, N-0401 Oslo (NO).

(71)(72) Applicant and Inventor *(for GB only)*: COCKBAIN, Julian [GB/GB]; 27 Ladbroke Road, London W11 3PD (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MCINTIRE, Gregory, Lynn [US/US]; Nycomed Inc., 466 Devon Park Drive, Wayne, PA 19087-8630 (US). TONER, John, Luke [US/US]; Nycomed Inc., 466 Devon Park Drive, Wayne, PA 19087-8630 (US). BACON, Edward, Richard [US/US]; Nycomed Inc., 466 Devon Park Drive, Wayne, PA 19087-8630 (US). HAYLEY, Patrick, Joseph [US/US]; Nycomed Inc., 466 Devon Park Drive, Wayne, PA 19087-8630 (US).

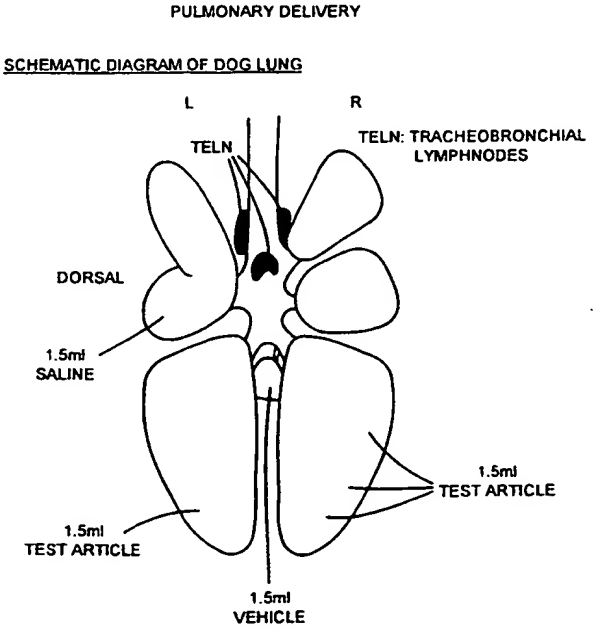
(74) Agents: COCKBAIN, Julian et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*

(88) Date of publication of the international search report:
12 August 1999 (12.08.99)

(54) Title: CONTRAST MEDIA FOR IMAGING OF LUNG DRAINING LYMPH NODES, ADMINISTERED THROUGH THE LUNGS




(57) Abstract

The invention relates to the use of particulate contrast media in the *in vivo* imaging of lung draining lymph nodes, e.g. to stage lung cancer patients.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | | | TR | Turkey |
| BG | Bulgaria | HU | Hungary | ML | Mali | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MN | Mongolia | UA | Ukraine |
| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | NZ | New Zealand | | |
| CM | Cameroon | | | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LI | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |

# INTERNATIONAL SEARCH REPORT

Intern ,nal Application No
PCT/GB 98/01489

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K49/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | EP 0 602 691 A (STERLING WINTHROP INC)<br>22 June 1994<br>see example 5 | 1-9 |
| | --- | |
| Y | WO 97 13503 A (SELVARAJ ULAGARAJ ;MESSING GARY L (US); PENN STATE RES FOUND (US))<br>17 April 1997 | 1-6,9 |
| X | see examples | 7,8 |
| | --- | |
| Y | WO 96 25918 A (NANOSYSTEM LLC)<br>29 August 1996 | 1-6,9 |
| X | see example 2 | 7,8 |
| | --- | |
| Y | EP 0 498 482 A (STERLING WINTHROP INC)<br>12 August 1992<br>see example 9 | 1-9 |
| | --- | |
| | -/-- | |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 10 November 1998 | 06. 04. 99 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | DULLAART A.W.M. |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 98/01489

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5 525 328 A (BACON EDWARD R ET AL)<br>11 June 1996<br>cited in the application<br>see examples 9,10<br>see column 7, line 32 - line 42 | 1-9 |
| X | EP 0 387 154 A (PF MEDICAMENT)<br>12 September 1990<br>see figures 3A,6-8<br>see examples 6,7 | 1-9 |
| Y | US 4 911 690 A (WEINSTEIN JOHN ET AL)<br>27 March 1990<br>see example 2 | 1-9 |
| Y | THIELE J ET AL: "Computerized tomography measurement of lung ventilation by inhalation of Isovist-300]"<br>RONTGENPRAXIS, SEP 1995, VOL. 48, NO. 9, PAGE(S) 259-60, XP002083900<br>see abstract<br>see paragraph AUSWERTUNG | 1-6,9 |
| Y | WENZEL-HORA BI ET AL: "Iotasul, a water-soluble (non-oily) contrast medium for direct and indirect lymphography: radiological and morphological investigations in dogs."<br>LYMPHOLOGY, SEP 1981, VOL. 14, NO. 3, PAGE(S) 101-12, XP002083901<br>see abstract<br>see paragraph DISCUSSION | 1-9 |
| Y | MORGAN HK ET AL: "Inhalation of 2,3,5-triiodobenzoic acid by normal and sulfur dioxide-exposed rats."<br>J PHARM SCI, NOV 1974, VOL. 63, NO. 11, PAGE(S) 1759-61, XP002083902<br>see the whole document | 1-6,9 |
| A | BORCHARDT, G. ET AL: "Body distribution of 75Se-radiolabeled silica nanoparticles covalently coated with.omega.-functionalized surfactants after intravenous injection in rats"<br>J. DRUG TARGETING, 1994, VOL. 2, NO. 1, PAGES 61-77, XP002083903<br>see tables<br>see page 72, right-hand column | 1-9 |

-/--

1

# INTERNATIONAL SEARCH REPORT

Intern ..al Application No
PCT/GB 98/01489

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y,P | DAVIS S S: "Biomedical applications of nanotechnology - implications for drug targeting and gene therapy" TRENDS IN BIOTECHNOLOGY, vol. 15, no. 6, June 1997, page 217-224 XP004064510 see page 222, right-hand column - page 223 ----- | 1-9 |

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/GB 98/ 01489

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-9

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/ GB 98/01489

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-9

   Method of in vivo imaging of lung draining lymph nodes, and compositions/agents used in this method.

2. Claims: 10-12

   Pharmaceutical composition containing an anticancer agent and a contrast agent, and its use in a method of treatment by direct instillation into the lung.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten nal Application No
PCT/GB 98/01489

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0602691 A | 22-06-1994 | AU 673535 B | 14-11-1996 |
| | | AU 4732393 A | 30-06-1994 |
| | | CA 2107164 A | 16-06-1994 |
| | | CZ 9302401 A | 13-07-1994 |
| | | FI 934713 A | 16-06-1994 |
| | | HU 67446 A | 28-04-1995 |
| | | JP 6192067 A | 12-07-1994 |
| | | MX 9305804 A | 30-06-1994 |
| | | NO 933653 A | 16-06-1994 |
| | | NZ 248650 A | 26-08-1994 |
| | | SK 131293 A | 06-07-1994 |
| WO 9713503 A | 17-04-1997 | EP 0862420 A | 09-09-1998 |
| WO 9625918 A | 29-08-1996 | AU 4990696 A | 11-09-1996 |
| | | CA 2213638 A | 29-08-1996 |
| | | EP 0810853 A | 10-12-1997 |
| EP 0498482 A | 12-08-1992 | US 5145684 A | 08-09-1992 |
| | | AU 642066 B | 07-10-1993 |
| | | AU 1014592 A | 30-07-1992 |
| | | AU 654836 B | 24-11-1994 |
| | | AU 1014792 A | 30-07-1992 |
| | | CA 2059431 A | 26-07-1992 |
| | | CA 2059432 A | 26-07-1992 |
| | | EP 0499299 A | 19-08-1992 |
| | | FI 920321 A | 26-07-1992 |
| | | FI 920322 A | 26-07-1992 |
| | | IL 100754 A | 16-10-1996 |
| | | IL 100755 A | 08-12-1995 |
| | | JP 4317053 A | 09-11-1992 |
| | | JP 4295420 A | 20-10-1992 |
| | | MX 9200291 A | 01-10-1992 |
| | | MX 9200292 A | 01-10-1992 |
| | | NO 303668 B | 17-08-1998 |
| | | RU 2074002 C | 27-02-1997 |
| | | RU 2066553 C | 20-09-1996 |
| | | US 5451393 A | 19-09-1995 |
| | | US 5494683 A | 27-02-1996 |
| | | US 5552160 A | 03-09-1996 |
| | | US 5399363 A | 21-03-1995 |
| | | US 5318767 A | 07-06-1994 |
| US 5525328 A | 11-06-1996 | AU 2770395 A | 19-01-1996 |
| | | CA 2193389 A | 04-01-1996 |
| | | EP 0772457 A | 14-05-1997 |
| | | FI 965095 A | 18-12-1996 |
| | | JP 10502082 T | 24-02-1998 |
| | | NO 965454 A | 18-12-1996 |
| | | WO 9600089 A | 04-01-1996 |
| EP 0387154 A | 12-09-1990 | FR 2644059 A | 14-09-1990 |
| | | AT 88643 T | 15-05-1993 |
| | | AU 626645 B | 06-08-1992 |
| | | AU 5111490 A | 13-09-1990 |
| | | CA 2011772 A | 08-09-1990 |
| | | DK 387154 T | 24-05-1993 |
| | | ES 2054282 T | 01-08-1994 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/01489

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0387154 A | | JP 3236332 A | 22-10-1991 |
| | | US 5362474 A | 08-11-1994 |
| US 4911690 A | 27-03-1990 | NONE | |